Primary prevention of CVD: modification of diet in people with hypertension

Search date October 2013

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ABSTRACT

INTRODUCTION: Hypertension (persistent diastolic blood pressure of 90 mmHg or greater or systolic blood pressure 140 mmHg or greater) affects 20% to 35% of the world's adult population and increases the risk of cardiovascular disease, end-stage renal disease, and mortality. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of selected dietary modification for people with hypertension? We searched: Medline, Embase, The Cochrane Library, and other important databases up to October 2013 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 669 studies. After deduplication and removal of conference abstracts, 464 records were screened for inclusion in this overview. Appraisal of titles and abstracts led to the exclusion of 376 studies and the further review of 88 full publications. Of the 88 full articles evaluated, three systematic reviews and three RCTs were added. We performed a GRADE evaluation for eight PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for five interventions based on information about the effectiveness and safety of calcium supplements, a low-salt diet (including the DASH diet), magnesium supplements, a Mediterranean diet, and potassium supplements.

QUESTIONS

INTERVENTIONS

DIETARY SUPPLEMENTS

Likely to be beneficial

Unknown effectiveness

Footnote

* Categorisation decision influenced by data from a large meta-analysis not meeting the specific inclusion criteria for this overview.

Key points

- Hypertension (persistent diastolic blood pressure of 90 mmHg or greater or systolic blood pressure 140 mmHg or greater) affects 20% to 35% of the world's adult population, and increases the risk of cardiovascular disease, end-stage renal disease, and mortality.
- The rising rates of hypertension globally are thought to be due, at least in part, to poor diet and high salt intake. The intake of fruits and vegetables is low, with national surveys showing less than 30% of Western populations consuming the recommended five servings daily. The average salt intake in many countries ranges from 3.4 to 12.0 g per day. Numerous guideline bodies advocate dietary modification and salt restriction in concert with other health behaviours to lower blood pressure and reduce cardiovascular risk.
- Previous versions of this overview evaluated the evidence for the effects of dietary modification, as well as different antihypertensive drugs for people with hypertension. For this update, we have focused on the evidence from RCTs and systematic reviews of RCTs on selected dietary modifications in people with hypertension.
- We found no RCT evidence assessing whether dietary modification reduces morbidity or mortality from hypertension compared with a normal diet.

  Mediterranean-style diets may be more effective at reducing blood pressure compared with no or minimal intervention in people with hypertension.

  A low-salt diet may reduce blood pressure compared with usual diets in people with hypertension.

  We included the DASH diet within this low-salt diet option. The DASH diet contains other elements that may potentially reduce blood pressure (such as high potassium levels).

  We do not know whether supplementation with magnesium or calcium is effective in reducing blood pressure.

  Potassium supplementation may be more effective in reducing blood pressure compared with placebo or no supplementation in people with hypertension. A large meta-analysis, which did not meet *BMJ Clinical Evidence* inclusion criteria for this overview, found that both increased dietary potassium intake and potassium supplementation were associated with reduced blood pressure in people with hypertension.

  Combinations of potassium plus calcium, potassium plus magnesium, and calcium plus magnesium may be no more effective than no supplementation in reducing blood pressure.
- RCTs may only provide limited evidence on longer-term outcomes, such as mortality or cardiovascular events, due to the restricted numbers included in most trials and the length of follow-up needed to identify any differences between groups. Large observational studies may provide important evidence on these longer term outcomes.

Clinical context

GENERAL BACKGROUND

Hypertension (persistent diastolic blood pressure of 90 mmHg or greater or systolic blood pressure 140 mmHg or greater) affects 20% to 35% of the world's adult population and increases the risk of cardiovascular disease, end-stage renal disease, and mortality. Dietary modification is important to consider because it has the potential to reduce blood pressure independently from antihypertensive drugs. In patients treated with drugs, successful dietary modification can lead to dose or medication reductions. In addition, dietary modification may have benefits over and above blood pressure reduction, such as improvements in health-related quality of life. [1]

FOCUS OF THE REVIEW

Dietary modification is an important potential treatment for hypertension. Dietary modifications that are effective and safe can improve blood pressure control and reduce the need for antihypertensive drugs. If dietary modifications are made as a component of an overall commitment to a healthier lifestyle, improvements beyond blood pressure reduction could potentially be realised. There are many diets that have been considered for people with hypertension, including low fat and low carbohydrate diets, weight-reducing, and vegetarian diets, but we have focused on the following selected dietary modifications for this update: low-salt (including the DASH diet); Mediterranean-style diets; and supplementary calcium, magnesium, or potassium.

COMMENTS ON EVIDENCE

RCTs and systematic reviews of RCTs were evaluated in this overview for establishing efficacy of selected dietary interventions. Hard clinical endpoints were preferred. However, there were, overall, few studies examining the effect of dietary modification on cardiovascular disease endpoints and mortality. Thus, the majority of evidence presented here relates to changes in blood pressure, though this is an established surrogate for cardiovascular disease and cardiovascular deaths.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this overview was carried out from the date of the last search, December 2007, to October 2013. A back search from 1966 was performed for the new options added to the scope at this update. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 669 studies. After deduplication and removal of conference abstracts, 464 records were screened for inclusion. Appraisal of titles and abstracts led to the exclusion of 376 studies and the further review of 88 full publications. Of the 88 full articles evaluated, three systematic reviews and three RCTs were added at this update.

DEFINITION Hypertension, a clinically important elevation in blood pressure, is usually defined in adults as a diastolic blood pressure of 90 mmHg or greater, or a systolic blood pressure of 140 mmHg or greater, or use of antihypertensive drugs required to achieve a blood pressure lower than these levels. [2] [3] The WHO defines grade 1 hypertension as systolic blood pressures ranging from 140 to 159 mmHg systolic or 90 to 99 mmHg diastolic, grade 2 hypertension as pressures of 160 to 179 mmHg systolic or 100 to 109 mmHg diastolic, and grade 3 hypertension as pressures 180 mmHg or greater systolic or 110 mmHg diastolic. [2] Systematic reviews consistently show that treating essential hypertension (namely the elevation of systolic and diastolic blood pressures, in isolation or combination, with no secondary underlying cause) with antihypertensive drugs reduces fatal and non-fatal stroke, cardiac events, and total mortality compared with placebo in those with severe hypertension or high cardiovascular risk owing to age or other comorbid risk factors. [4] [5] [6] There is considerable interest in evaluating the role of non-pharmacological therapy in reducing blood pressure, especially as lifestyle factors are significantly associated with the development of essential hypertension. The rising rates of hypertension globally are thought to be due, at least in part, to poor diet and high salt intake. Intake of fruits and vegetables is low, with national surveys showing less than 30% of Western populations consuming the recommended five servings daily. [7] [8] The average salt intake in many countries ranges from 3.4 to 12.0 g per day. Higher sodium intakes, estimated by spot urine measures, are associated with higher blood pressure particularly in older adults and people with hypertension. [9] Estimated sodium intakes of 6 g or more per day in people with hypertension were associated with increased cardiovascular events. [10] Numerous guideline bodies advocate dietary modification and salt restriction in concert with other health behaviours to lower blood pressure and reduce cardiovascular risk. This overview, therefore, focuses on the effect of treating hypertension with dietary modifications compared with placebo, normal diet, or other treatment options included in this overview. Dietary modification is important to consider because it has the potential to reduce blood pressure without the need for antihypertensive drugs. In patients treated with drugs, successful dietary modification can lead to dose or medication reductions. In addition, dietary modification may have benefits over and above blood pressure reduction, such as improved health-related quality of life. [1] This overview includes studies on people with essential hypertension but with no diagnosis of coronary heart disease, renal disease, peripheral vascular disease (PVD), angina, stroke, transient ischaemic attack (TIA), myocardial infarction (MI), or heart failure. This overview excludes studies that only included people with diabetes. **Diagnosis** It is usually recommended that clinicians diagnose hypertension only after obtaining at least two elevated blood pressure readings at each of at least two separate visits over a period of at least 1 week. [3] This recommendation follows the pattern of blood pressure measurement in the RCTs of antihypertensive treatment, and represents a compromise between reliable detection of elevated blood pressure and clinical practicality.

INCIDENCE/ PREVALENCE

High blood pressure is the leading cause of death and disability in the world. [11] It affects 20% to 35% of adults aged 25 years or older globally. [12] The incidence of hypertension is higher in developing countries than developed countries and more prevalent in certain ethnic groups than others. The incidence of hypertension is expected to increase globally by 60% by the year 2025 due to rapid nutritional shifts, increasing life expectancies, and population growth. [13] [14]

AETIOLOGY/ RISK FACTORS

Identified risk factors for hypertension include advancing age, sex, poor diet, excess salt intake, excess alcohol intake, physical inactivity, stress, obesity, obstructive sleep apnoea, chronic kidney disease and underlying genetic predisposition, and psychological and social characteristics. [15] In addition, certain ethnic groups, such as non-Hispanic black people, are at higher risk of hypertension and earlier onset of hypertension. [16]

PROGNOSIS

People with hypertension have a two- to four-times increased risk of stroke, MI, heart failure, and peripheral vascular disease than those without hypertension. [17] Additionally, they have an increased risk of dementia, end-stage renal disease, retinopathy, aortic aneurysm, and early mortality. [18] [19] [20] [21] [22] The relative risk of adverse events associated with hypertension is continuous and graded. [17] The absolute risk of adverse outcomes from hypertension can be multiplied in the presence of other cardiovascular risk factors, including smoking, diabetes, and abnormal blood lipid levels, as well as the degree of blood pressure elevation. [23] Even modest elevations in blood pressure in young adulthood are associated with increased risk of cardiovascular events in middle age. [24]

AIMS OF INTERVENTION

To reduce morbidity and mortality from hypertension, with minimum adverse effects.

OUTCOMES

Mortality (all cause and cardiovascular); **cardiovascular events** (incidence of fatal and non-fatal cardiovascular events including coronary, cerebrovascular, renal, and heart failure); **surrogate outcomes** (includes change in levels of individual risk factors, such as **blood pressure**, that we only report when morbidity- and mortality-related outcomes are not available); **adverse effects**.

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal date October 2013. Databases used to identify studies for this systematic overview include: Medline 1966 to October 2013, Embase 1980 to October 2013, The Cochrane Database of Systematic Reviews 2013, issue 10 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this systematic overview were systematic reviews and RCTs published in English, at least single-blinded, and containing more than 20 individuals, of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed *a priori* with our expert contributor. In consultation with the expert contributor, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our pre-defined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' sections (see below). **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have removed the following previously reported question: What are the effects of different antihypertensive drugs for people with hypertension? For the question: What are the effects of selected dietary modification for people with hypertension?, we have removed the option Fish oil supplement and added the new option Meditarranean-style diet. **Data and quality** To aid readability of the numerical data in our overviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this overview (see table, p 15). The categorisation of the evidence (high, moderate, low, very low) reflects the quality of the evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *BMJ Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. Further details of how we perform the GRADE evaluation and the scoring system we use can be found on our website (http://clinicalevidence.bmj.com).

QUESTION **What are the effects of selected dietary modification in people with hypertension?**

OPTION **MEDITERRANEAN-STYLE DIET** New

Blood pressure
Mediterranean-style diet compared with normal diet Mediterranean-style diets may be more effective at reducing blood pressure compared with no or minimal intervention (i.e., normal diet) in people with hypertension (low-quality evidence). Note: we found no direct information from RCTs about the effects of Mediterranean diet on mortality or cardiovascular events in people with hypertension.

For GRADE evaluation of interventions for primary prevention of CVD: treating hypertension, see table, p 15 .

Benefits:

Mediterranean diet versus normal diet:
Mortality
We found one systematic review (search date 2012), [25] which found no RCTs that assessed the effect of Mediterranean diet versus normal diet on mortality.

Cardiovascular events
We found one systematic review (search date 2012), [25] which found no RCTs that assessed the effect of Mediterranean diet versus normal diet on cardiovascular events.

Blood pressure
We found one systematic review (search date 2012, 11 RCTs, 52,044 people), which found two RCTs (275 people) assessing the effect of Mediterranean diet versus control (no intervention or minimal intervention [i.e., maintenance of usual diet]) on blood pressure. [25] The first RCT (95 overweight or obese people with untreated hypertension; systolic blood pressure 130–159 mmHg, diastolic blood pressure 85–99 mmHg) found that a Mediterranean diet significantly reduced mean change from baseline in systolic (–11.2 mmHg with Mediterranean diet *v* –3.4 mmHg with no intervention: mean difference –7.80 mmHg, 95% CI –12.11 to –3.49; P value not reported) and diastolic (–7.5 mmHg with Mediterranean diet *v* –3.8 mmHg with control: mean difference –3.70 mmHg, 95% CI –6.10 to –1.30; P value not reported) blood pressures compared with control at 4 months. The second RCT (180 people with metabolic syndrome and elevated blood pressure 130/85 mmHg or higher) found that a Mediterranean diet significantly reduced mean change from baseline in systolic (–4 mmHg with Mediterranean diet *v* –1 mmHg with minimal intervention: mean difference –3.00 mmHg, 95% CI –3.46 to –2.54; P value not reported) and diastolic (–3 mmHg with Mediterranean diet *v* –1 mmHg with minimal intervention: mean difference –2.00 mmHg, 95% CI –2.29 to –1.71; P value not reported) blood pressures compared with minimal intervention (general advice) at 2 years.

Harms:

The review gave no information on adverse effects. [25]

Comment: All RCTs included in the review (11 RCTs) presented data on dietary advice to follow a Mediterranean-style diet for the primary prevention of cardiovascular disease in people with and without hypertension. The authors of the review did not carry out a meta-analysis because of substantial heterogeneity identified across the studies and because of the small trial effect differences observed between fixed- and random-effects models. Data relating specifically to people with hypertension were limited to two RCTs out of the 11 RCTs included in the review. Level of masking of participants and key personnel in the identified RCTs were unclear. [25]

Although observational studies demonstrate that those with greater adherence to a Mediterranean style diet have lower mortality and development of CVD, [26] our overview did not identify any randomised trials evaluating these endpoints in patients with hypertension. In the Women's Health Initiative, 48,835 post-menopausal women (43% had a previous diagnosis of hypertension) were randomised to intensive behaviour modification to reduce total fat intake, increase fruit and vegetable intake to five servings/day, and increase grains to six servings/day, or usual diet. After a 6-year follow-up, there was no significant difference in the incidence in coronary heart disease or stroke between the groups. [27]

Since the date of this overview, however, the PREDIMED trial results were published. [28] The trial included 7447 men and women aged between 55 and 80 years who were at high risk for CVD (82% had hypertension). The participants were randomised to a Mediterranean-style diet (MD) supplemented with extra-virgin olive oil (MD+EVOO), MD supplemented with mixed nuts (MD+nuts: walnuts, almonds, and hazelnuts), or the control diet (low-fat diet). After a mean of 4.8 years follow-up, patients randomised to the MD had significantly lower risk of major cardiovascular endpoints (myocardial infarction, stroke, or cardiovascular death). Collectively, these studies indicate that a Mediterranean-style diet is likely to be beneficial based on evidence for blood pressure lowering and some emerging evidence on cardiovascular benefits in high-risk patients.

Clinical guide
Mediterranean-style diets typically include a higher than usual intake of fruit, vegetables, whole grains, and unsaturated fatty acids, lower consumption of red meat, greater consumption of fish, and moderate intake of dairy products.

OPTION LOW-SALT DIET (INCLUDING THE DASH DIET)

Blood pressure
Low-salt diet compared with usual salt intake Low-salt diets seem more effective at reducing blood pressure compared with usual diets in people with hypertension (low-quality evidence). Note: we also included the DASH diet within this low-salt diet option. The DASH diet contains other elements that may potentially reduce blood pressure (such as higher potassium levels). We found no direct information from RCTs about the effects of actual dietary sodium reduction (rather than advice to reduce sodium) on mortality or cardiovascular events in people with hypertension.

For GRADE evaluation of interventions for primary prevention of CVD: treating hypertension, see table, p 15 .

Benefits: **Low salt versus usual salt intake:**
Mortality
We found no systematic review or RCTs examining the effect of actual sodium reduction (rather than advice to reduce sodium) on mortality in people with hypertension.

Cardiovascular events
We found no systematic review or RCTs examining the effect of actual sodium reduction (rather than advice to reduce sodium) on cardiovascular events in people with hypertension.

Blood pressure
We found one systematic review (search date 2012, 22 RCTs, 990 people with hypertension), which assessed the effect of salt reduction on blood pressure. [29] We also found one subsequent RCT [30] and one additional RCT. [31]

The systematic review found that a 75 mmol reduction in daily salt intake (range –117 mmol to –53 mmol) significantly reduced blood pressure compared with patients in the usual salt intake (median 9.5 g/day) group over a median 5 weeks (range 4 weeks to 1 year; 21 RCTs, 966 people; mean difference in systolic blood pressure: –5.39 mmHg, 95% CI –6.62 mmHg to –4.15 mmHg; P <0.00001; I^2 = 61%, P = 0.00018; mean difference in diastolic blood pressure: –2.82 mmHg, 95% CI –3.54 to –2.11 mmHg; P <0.00001; I^2 = 52%, P = 0.002). [29] These differences were observed in white and black patients, as well as women and men. Importantly, one RCT included in the review (412 people with systolic/diastolic blood pressure over 120/80 mmHg, mean age 48 years, duration 30 days) directly assessed the relationship between sodium and blood pressure levels. [32] People were assigned to receive prepared food with three different target levels of sodium intake (150, 100, and 50 mmol/day [8.6, 5.7, and 2.9 g/day]) in a crossover design. [32] The RCT found that, for people eating a typical American diet, those in the lowest salt-intake group (i.e., those with the greatest salt restriction) had significantly reduced systolic (mean difference –6.7 mmHg, 95% CI –8.0 mmHg to –5.4 mmHg; P <0.001) and diastolic (mean difference –3.5 mmHg, 95% CI –4.3 mmHg to –2.6 mmHg; P <0.001) blood pressures compared with those with the highest salt intake. Although the greatest effect of salt reduction occurred after 1 week, blood pressures continued to decline throughout the duration of the study, suggesting that effects may be greater with longer-term follow-up. [33]

The subsequent RCT (462 people from 200 families in rural China, including a subgroup of 237 people with hypertension; systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg; antihypertensive pre-treatment status not reported) assessed the effect of salt substitution versus normal salt on blood pressure. [30] The RCT found that salt substitution (65% sodium chloride, 25% potassium chloride, and 10% magnesium sulfate) significantly reduced systolic blood pressure compared with normal salt diet (100% sodium chloride) during 24 months in people with hypertension (mean difference –4 mmHg, 95% CI –2 mmHg to –6 mmHg; P <0.05). However, there was no significant difference between groups in change in diastolic blood pressure during 24 months (mean difference: –0 mmHg, 95% CI –1 mmHg to +1 mmHg; P = 0.66). [30]

The additional RCT (92 residents of a Cape Town township aged 50–75 years and with drug-treated mild-to-moderate hypertension; systolic blood pressure 160 mmHg or lower, diastolic blood pressure 95 mmHg or lower) compared a modified cation content low-sodium diet (70 mmol reduction in daily sodium intake with increased potassium, calcium, and magnesium) with a control diet (in which the same foods were provided but of a standard commercial composition allowing for blinding). [31] The RCT found that the low-salt diet significantly reduced systolic blood pressure compared with the control diet (final blood pressure evaluated as a mean of values recorded at weeks 4 and 8; mean difference: –6.19 mmHg, 95% CI –11.44 mmHg to –0.94 mmHg; P = 0.021). However, there was no significant difference between groups in diastolic blood pressure (mean difference: –0.60 mmHg, 95% CI –3.02 mmHg to +1.83 mmHg; P = 0.626). The authors noted that the largest effect occurred within the first 4 weeks of the intervention, with no significant difference in the change from baseline in systolic and diastolic blood pressure between weeks 4 and 8. [31]

Harms: None of the included studies gave any information on adverse effects. [29] [30] [31] Please see Comment section for further information on adverse effects.

Comment: Small RCTs tended to report larger reductions in systolic and diastolic blood pressure than larger RCTs. This may be explained by publication bias or less-rigorous methodology in small RCTs.

In both the subsequent and additional RCTs, the group randomised to reduced-salt diet received a salt substitute that, although lower in sodium chloride, included potassium, magnesium, and calcium salts. Consequently, people allocated to reduced salt are also receiving supplemental potassium, magnesium, and calcium, which are interventions of interest to this overview. In the subsequent RCT, people receiving reduced salt (65% sodium chloride) also received potassium (25% potassium chloride) and magnesium (10% magnesium sulfate). [30] In the additional RCT, compared with standard salt, the salt substitute comprised 41% less sodium, 826% more potassium, 388% more calcium, and 368% more magnesium. [31]

The systematic review also evaluated change in systolic and diastolic blood pressure data by the subgroups of ethnicity and sex. [29] The review found that, compared with usual salt intake, reduced salt intake significantly reduced diastolic blood pressure in men and women and in both ethnicities evaluated (white and black). The review carried out a sensitivity analysis to explore heterogeneity and investigated the effects of age (mean age of participants in individual trials), ethnicity (proportion of whites as a continuous variable), and the change in 24-hour urinary sodium. Results showed that ethnicity and 24-hour urinary sodium were significantly associated with the fall in systolic blood pressure. Together, age, ethnicity, and change in 24-hour urinary sodium accounted for 46% of the variance in systolic blood pressure among studies. For diastolic blood pressure, none of the three variables was significantly associated with the fall in diastolic blood pressure; the three variables accounted for 11% of the variance across studies. [29]

Adverse effects

The TONE trial studied people with blood pressure that was controlled on only one or two antihypertensive agents and found no significant harms with reduced sodium intake. Similarly the TOHP studies (phases 1 and 2) in patients with high-normal blood pressure found no significant harms with sodium reduction. [34] [35] [36] Please see the *BMJ Clinical Evidence* overview on Primary prevention of CVD: diet for further detail.

Clinical guide
We note that a Dietary Approaches to Stop Hypertension (DASH) diet is naturally low in sodium and high in potassium, magnesium, and calcium. A DASH diet is recommended for people with hypertension; if this diet is followed, the incremental effect of further sodium reduction is small (1.7/1.0 mmHg). [32]

OPTION	CALCIUM SUPPLEMENTATION

Blood pressure
Calcium supplementation compared with placebo or no supplementation Calcium supplements may reduce systolic blood pressure by small amounts, but we don't know whether calcium supplementation reduces diastolic blood pressure (very low-quality evidence).

Calcium plus magnesium supplementation compared with placebo Calcium plus magnesium supplementation may be no more effective than placebo at reducing systolic and diastolic blood pressure at 24 weeks (low-quality evidence).

Calcium plus potassium supplementation compared with placebo Calcium plus potassium supplementation may be no more effective than placebo at reducing systolic and diastolic blood pressure at 24 weeks (low-quality evidence). Note: we found no direct information from RCTs about the effects of calcium supplementation on mortality or cardiovascular events in people with hypertension.

For GRADE evaluation of interventions for primary prevention of CVD: treating hypertension, see table, p 15 .

Benefits: **Calcium supplementation versus placebo or no supplementation:**
Mortality
We found no systematic review or RCTs examining the effects of calcium supplementation on mortality in people with primary hypertension.

Cardiovascular events
We found no systematic review or RCTs examining the effects of calcium supplementation on cardiovascular events in people with primary hypertension.

Blood pressure
We found two systematic reviews (search date 2003) [37] [38] assessing the effects of calcium supplementation on blood pressure. The reviews had different inclusion criteria, included different RCTs in their meta-analysis, and found slightly different results, and so we discuss both reviews. The first review included clinical trials and RCTs with a minimum length of follow-up of 2 weeks (range of follow-up of identified RCTs was 2 to 208 weeks). The second review specified a minimum follow-up of 8 weeks, and systolic blood pressure of 140 mmHg or greater or diastolic blood pressure of 85 mmHg or greater with no known primary cause. [38] The review excluded RCTs in which changes were made to antihypertensive drugs received during the course of the trial.

The first review (40 RCTs, 2492 people) assessed the effects of calcium supplementation on blood pressure. [37] Meta-analysis of RCTs in people with hypertension (defined by the review as initial blood pressure of 140/90 mmHg or greater) found that, compared with placebo or no treatment, calcium supplementation (mean daily dose of 1200 mg) significantly reduced systolic and diastolic blood pressure at 2–208 weeks (23 RCTs, 764 people with hypertension: mean difference in change in systolic blood pressure from baseline: –2.17 mmHg, 95% CI –3.78 mmHg to –0.55 mmHg; mean difference in change in diastolic blood pressure from baseline: –0.95 mmHg, 95% CI –1.89 mmHg to –0.01 mmHg).

The second review in people with hypertension (13 RCTs [all of which were identified by the first review], 485 people) found that, compared with control (placebo, no treatment, or usual care), calcium supplementation significantly reduced systolic blood pressure at 8 to 15 weeks (mean difference –2.53 mmHg, 95% CI –4.45 mmHg to –0.60 mmHg). [38] However, the review found no significant difference between groups in diastolic blood pressure at 8 to 15 weeks (mean difference –0.81 mmHg, 95% CI –2.07 mmHg to +0.44 mmHg). The review reported moderate heterogeneity among RCTs in the analyses of diastolic blood pressure (P = 0.06 for diastolic blood pressure; level of statistical significance for heterogeneity not specified). Sensitivity analyses suggested that the poor quality of the identified RCTs (unclear level of blinding and non-reporting of standard deviation of results) was a source of heterogeneity. Percentage of people with CVD was zero in most RCTs, but some RCTs did not report the proportion of people with CVD. Subgroup analyses based on calcium dose and baseline blood pressure found similar results for treatment effect, which suggested that dose of calcium and baseline blood pressure were not contributing to the heterogeneity. The review commented that, because of the poor quality of the RCTs, results of the meta-analysis should be interpreted with caution.

Calcium plus magnesium supplementation versus placebo:
We found one systematic review (search date 2003), [39] which identified one four-armed RCT (140 people with hypertension, mean baseline systolic and diastolic blood pressures of 139 mmHg and 90 mmHg, respectively) assessing the effects of supplementation with mineral combinations on blood pressure. [40] The RCT compared potassium (60 mmol) plus calcium (25 mmol; 29 people) with potassium plus magnesium (15 mmol; 31 people) with calcium plus magnesium (34 people) and with placebo (31 people); see option on Potassium supplementation, p 9 for data on comparisons involving potassium. The RCT found no significant difference between supplementation with calcium plus magnesium and placebo in change from baseline in either systolic (mean difference +2.1 mmHg, 95% CI –1.8 mmHg to +6.0 mmHg) or diastolic (mean difference +2.2 mmHg, 95% CI –1.0 mmHg to +5.4 mmHg) blood pressure at 24 weeks.

Calcium plus potassium supplementation versus placebo:
See Benefits of Potassium supplementation, p 9 .

Harms:

Calcium supplementation versus placebo or no supplementation:
The first review gave no information on adverse effects. [37] The second systematic review found no significant difference between calcium supplementation and control in proportion of people withdrawing from a trial or in rate of gastrointestinal adverse effects, including diarrhoea (withdrawal from trial: 3 RCTs, 161 people: any reason for withdrawal: 5/87 [6%] with calcium supplementation *v* 5/74 [7%] with control; RR 0.96, 95% CI 0.30 to 3.08; rate of gastrointestinal adverse effects, including diarrhoea: 3 crossover RCTs, 178 people: 7/89 [8%] with calcium supplementation *v* 8/89 [9%] with control; RR 0.82, 95% CI 0.31 to 2.14). [38]

Calcium plus magnesium supplementation versus placebo:
The RCT gave no information on adverse effects. [40]

Calcium plus potassium supplementation versus placebo:
See Harms of Potassium supplementation, p 9 .

Comment:

Data relating specifically to people with hypertension are limited by few studies with small sample sizes and short durations.

Clinical guide
Calcium supplements should not routinely be used to lower blood pressure given the availability of other agents that have demonstrated effectiveness.

OPTION MAGNESIUM SUPPLEMENTATION

Blood pressure
Magnesium supplementation compared with placebo or no supplements Magnesium supplementation may be no more effective than placebo or no supplements at reducing systolic blood pressure in people with hypertension, but we don't know whether magnesium supplementation is more effective at reducing diastolic blood pressure (very low-quality evidence).

Magnesium plus potassium supplementation compared with control Magnesium plus potassium supplementation seems no more effective than control (placebo, no treatment, or usual care) at reducing blood pressure at 24 to 28 weeks (moderate-quality evidence).

Magnesium plus calcium supplementation compared with placebo Magnesium plus calcium supplementation may be no more effective than placebo at reducing blood pressure at 24 weeks (low-quality evidence). Note: we found no direct information from RCTs about the effects of magnesium supplementation on mortality or cardiovascular events in people with hypertension.

For GRADE evaluation of interventions for primary prevention of CVD: treating hypertension, see table, p 15 .

Benefits:

Magnesium versus placebo or no supplementation:
Mortality
We found no systematic review or RCTs examining the effects of magnesium supplementation on mortality.

Cardiovascular events
We found no systematic review or RCTs examining the effects of magnesium supplementation on cardiovascular events.

Blood pressure

We found two systematic reviews, which between them identified 18 RCTs assessing the effects of supplementation with magnesium on blood pressure. [41] [42] The reviews had different inclusion criteria, included different RCTs in their meta-analyses, and found slightly different results, and so we discuss both reviews. The first review included RCTs of any length of follow-up (range of follow-up of identified RCTs was 3 to 24 weeks), and RCTs in which concomitant antihypertensive medication was administered. [41] The second review specified a minimum follow-up of 8 weeks, and systolic blood pressure of 140 mmHg or greater or diastolic blood pressure of 85 mmHg or greater with no known primary cause. The review excluded RCTs in which changes were made to antihypertensive drugs received during the course of the trial. [42]

The first review (search date 2001, 20 RCTs, 1220 people with and without hypertension and with normal magnesium) compared the effects of magnesium supplementation versus placebo on blood pressure. [41] The review performed a separate analysis of RCTs in people with hypertension (14 RCTs, 467 people, hypertension defined as average baseline systolic blood pressure over 140 mmHg or diastolic blood pressure over 90 mmHg). It found no significant difference between magnesium supplementation (increase of 10 mmol/day) and placebo at 3 to 24 weeks in reduction in systolic blood pressure (mean difference in change in systolic blood pressure from baseline: –3.3 mmHg, 95% CI –6.8 mmHg to +0.1 mmHg) or diastolic blood pressure (mean difference in change in diastolic blood pressure from baseline –2.3 mmHg, 95% CI –5.6 mmHg to +1.0 mmHg).

The second review in people with hypertension (search date 2006, 12 RCTs, 545 people), [42] which identified the first review, [41] found that, compared with control (placebo, no treatment, or usual care), magnesium supplementation significantly reduced diastolic blood pressure at 8 to 26 weeks (12 RCTs [3 of crossover design], 671 people: mean difference –2.15 mmHg, 95% CI –3.40 mmHg to –0.90 mmHg; P = 0.00073; heterogeneity: I^2 = 47%, P = 0.03). [42] However, the review found no significant difference between groups in systolic blood pressure at 8 to 26 weeks (mean difference –1.26 mmHg, 95% CI –3.99 mmHg to +1.47 mmHg; P = 0.37; I^2 = 62%, P = 0.003). Percentage of people with CVD was zero in most RCTs, but some RCTs did not report the proportion of people with CVD. The review reported significant heterogeneity among RCTs in the analyses of systolic and diastolic blood pressure (P = 0.003 for systolic blood pressure and P = 0.03 for diastolic blood pressure). The review reported that subgroup analyses indicated heterogeneity was unlikely to be the result of variation in magnesium dose, baseline blood pressure, methods of measuring blood pressure, or proportion of men enrolled. Potential sources of heterogeneity that could not be subjected to subgroup analysis were use of antihypertensive medication and level of dietary sodium or magnesium.

Magnesium plus potassium versus control:

See Benefits of Potassium supplementation, p 9 .

Magnesium plus calcium versus control:

See Benefits of Calcium supplementation, p 7 .

Harms:

Magnesium versus placebo or no supplementation:

The first systematic review gave no information on adverse effects. [41] The second systematic review found no significant difference between magnesium supplementation and control in proportion of people experiencing an adverse effect or in rate of gastrointestinal adverse effects (any adverse effect: 6 RCTs, 330 people: 21/181 [12%] with magnesium supplementation *v* 19/149 [13%] with control; Risk Difference 0.01, 95% CI –0.04 to +0.06; gastrointestinal adverse effects: 3 RCTs, 245 people: 11/138 [8%] with magnesium supplementation *v* 7/107 [7%] with control; Risk Difference 0.00, 95% CI –0.05 to +0.05). [42]

Magnesium plus potassium versus control:

See Harms of Potassium supplementation, p 9 .

Magnesium plus calcium versus control:

See Harms of Calcium supplementation, p 7 .

Comment:

Larger studies with higher-dose magnesium supplementation are still needed.

Clinical guide

Magnesium supplementation has no current role in the treatment of hypertension.

OPTION POTASSIUM SUPPLEMENTATION

Blood pressure

Potassium supplementation compared with placebo or no supplementation Potassium may be more effective than placebo or no supplementation at reducing blood pressure (low-quality evidence).

Potassium plus calcium supplementation compared with placebo Potassium plus calcium supplementation may be no more effective than placebo at reducing systolic and diastolic blood pressure at 24 weeks (low-quality evidence).

Potassium plus magnesium supplementation compared with control Potassium plus magnesium supplementation seems no more effective than control (placebo, no treatment, or usual care) at reducing systolic and diastolic blood pressure at 24 to 28 weeks (moderate-quality evidence).

Adverse effects
Potassium supplements can increase serum potassium and need regular monitoring. Note: we found no direct information from RCTs about the effects of potassium supplementation on mortality or cardiovascular events in people with hypertension.

For GRADE evaluation of interventions for primary prevention of CVD: treating hypertension, see table, p 15 .

Benefits:

Potassium supplementation versus placebo or no supplementation:
Mortality
We found no systematic review or RCTs examining the effects of potassium supplementation on mortality in people with primary hypertension.

Cardiovascular events
We found no systematic review or RCTs examining the effects of potassium supplementation on cardiovascular events in people with primary hypertension.

Blood pressure
We found two systematic reviews (search dates 1995; [43] and 2005 [44]), one additional RCT, [45] and one subsequent RCT [46] assessing the effects of potassium supplementation on blood pressure. The reviews had different inclusion criteria, included different RCTs in their meta-analyses, and found different results, and so we discuss both reviews. The first review included open-label RCTs of any length of follow-up (range of follow-up of identified RCTs was 4 days to 3 years), and RCTs in which concomitant antihypertensive medication was administered, with the caveat that additional treatments were equal in treatment and control groups. [43] The second review specified a minimum follow-up of 8 weeks, and systolic blood pressure of 140 mmHg or greater or diastolic blood pressure of 85 mmHg or greater with no known primary cause. [44] The review excluded RCTs in which changes were made to antihypertensive drugs received during the course of the trial.

The first review (search date 1995, 21 RCTs, 1560 adults with hypertension, and 12 RCTs, 1005 people with normal blood pressure, age range across RCTs of 19–79 years), [43] which was identified by the second review, [44] assessed the effects of potassium supplementation in the prevention and treatment of hypertension. [43] Meta-analysis of RCTs in people with hypertension (baseline systolic and diastolic blood pressure not specified) found that, compared with placebo or no treatment, potassium supplementation significantly reduced systolic and diastolic blood pressure at 4 days to 24 weeks (20 RCTs, 1512 people with hypertension: mean difference in change in systolic blood pressure from baseline –4.4 mmHg, 95% CI –6.6 mmHg to –2.2 mmHg; mean difference in change in diastolic blood pressure from baseline –2.5 mmHg, 95% CI –4.9 mmHg to –0.1 mmHg). The mean reduction in systolic and diastolic blood pressure was larger in people with hypertension than in those with blood pressure in the normal range and in those patients consuming a high-salt diet. The authors of the review recommended potassium supplementation for the treatment of hypertension.

The second review (search date 2005, 6 RCTs [all of which were identified by the first review], 483 people with hypertension) found no significant difference between potassium supplementation and control (placebo, no treatment, or usual care) in reduction in systolic or diastolic blood pressure at 8 to 16 weeks, although the absolute mean difference between groups for both outcomes was large (5 RCTs, 398 people: systolic blood pressure: mean difference –11.25 mmHg, 95% CI –25.18 mmHg to +2.68 mmHg, P = 0.11; diastolic blood pressure: WMD –5.03 mmHg, 95% CI –12.47 mmHg to +2.42 mmHg, P = 0.19). [44] The review reported significant heterogeneity among RCTs in the analyses of systolic and diastolic blood pressure (P <0.0001 for both analyses). The review reported that the heterogeneity was unlikely to be the result of variation in methods of measuring blood pressure, and suggested unreported differences in study population (e.g., dietary potassium intake) as a source of heterogeneity. Percentage of people with CVD was zero in most RCTs, but some RCTs did not report the proportion of people with CVD. The authors of the review also commented that follow-up of some of the RCTs included in the meta-analysis may have been too short to draw conclusions on the effectiveness of potassium supplementation.

The additional RCT (150 adults living in China, aged 35–64 years, blood pressure 130–159/80–94 mmHg) found that, compared with placebo, supplementation with potassium chloride (60 mmol/day) significantly reduced systolic blood pressure at 12 weeks (mean difference –5 mmHg, 95% CI –7.88 mmHg to –2.13 mmHg). However, it found no significant difference in mean diastolic blood pressure between potassium chloride and placebo (mean difference –0.63 mmHg, 95% CI –2.49 mmHg to +1.23 mmHg). [45]

The subsequent RCT (46 adults living in the UK, mean age 51 years, blood pressure 145/91 mmHg) was a three-armed trial with a cross-over design comparing supplementation with potassium chloride (64 mmol/day) or potassium bicarbonate (64 mmol/day) with placebo. Pre-crossover results at 4 weeks found no significant difference in mean systolic (P = 0.344 among groups) or diastolic (P = 0.261 among groups) blood pressures (mean 145/91 mmHg on placebo, 142/90 mmHg on potassium chloride, and 144/90 mmHg on potassium bicarbonate, 42 people in this analysis). [46] See Comment section, p 9 for further discussion of trials not meeting *BMJ Clinical Evidence* inclusion criteria.

Potassium plus calcium supplementation versus placebo:
We found one systematic review (search date 2003), [39] which identified one four-armed RCT (140 people with hypertension, mean baseline systolic and diastolic blood pressures of 139 mmHg and 90 mmHg, respectively) assessing the effects of supplementation with mineral combinations on blood pressure. [40] The RCT compared potassium (60 mmol) plus calcium (25 mmol; 29 people) with potassium plus magnesium (15 mmol; 31 people) with calcium plus magnesium (34 people) and with placebo (31 people); see option on Calcium supplementation, p 7 for data on comparison of calcium plus magnesium with placebo (31 people). The RCT found no significant difference between supplementation with potassium plus calcium and placebo in change from baseline in either systolic (mean difference –0.7 mmHg, 95% CI –4.3 mmHg to +2.9 mmHg) or diastolic (mean difference –0.4 mmHg, 95% CI –2.9 mmHg to +2.1 mmHg) blood pressure at 24 weeks.

Potassium plus magnesium supplementation versus placebo:
We found one systematic review (search date 2003, 3 RCTs, 277 people with hypertension) assessing the effects of supplementation with combined potassium plus magnesium on blood pressure. [39] The review found no significant difference between supplementation with potassium plus magnesium and control (placebo, no treatment, or usual care) in reduction in systolic and diastolic blood pressure at 24 to 28 weeks, although there was a difference between groups in favour of mineral supplementation for both outcomes (3 RCTs: systolic blood pressure: mean difference –4.64 mmHg, 95% CI –9.94 mmHg to +0.66 mmHg, P = 0.086; diastolic blood pressure: mean difference –3.84 mmHg, 95% CI –9.47 mmHg to +1.79 mmHg, P = 0.18). The review reported significant heterogeneity among RCTs in the analyses of systolic and diastolic blood pressure (P = 0.04 for systolic blood pressure; P = 0.001 for diastolic blood pressure). Sources of heterogeneity were baseline characteristics of the people enrolled, methods of assessing blood pressure outcomes, and ingested dose and method of administration of mineral supplements. Sensitivity analysis using alternative reported values, which accounted for missing data, resulted in the change in systolic blood pressure becoming significant (mean difference –5.77 mmHg, 95% CI –10.53 mmHg to –1.02 mmHg, P = 0.017; heterogeneity across RCTs significant: I^2 = 75%, P = 0.02); the difference in diastolic blood pressure remained non-significant (mean difference –3.19 mmHg, 95% CI –7.58 mmHg to +1.20 mmHg, P = 0.15; heterogeneity across RCTs significant: I^2 = 84%, P = 0.002).

Harms:

Potassium supplementation versus placebo or no supplementation:
The systematic review [43] and subsequent RCT [45] gave no information on adverse effects. In the Cochrane review, [44] one trial reported minimal side effects with potassium supplementation, including abdominal discomfort.

Potassium plus calcium supplementation versus placebo:
Only mild adverse effects were reported. [40]

Potassium plus magnesium supplementation versus placebo:
The review found no significant difference between supplementation with potassium plus magnesium and control in proportion of people withdrawing from treatment (no further information on reasons for withdrawal given) (2 RCTs, 171 people: 8/85 [9%] with mineral supplement *v* 7/86 [8%] with control; Risk difference: –0.01, 95% CI –0.07 to +0.05). [39] The review stated that all three RCTs reported mild adverse effects associated with mineral supplementation, but two RCTs gave no further information on the types of adverse effect. Lack of information on adverse effects precluded pooling of data by the review.

Comment:

One systematic review, which included a meta analysis of 17 RCTs, did not meet *BMJ Clinical Evidence* inclusion criteria is included here in the Comment section because this is a large meta-analysis and the results are of clinical interest. It did not meet out inclusion criteria because it focused on potassium intake, not explicitly potassium supplementation; included people with and without hypertension (there was a lack of clarity on which interventions were used as comparisons for the subgroup analysis in people with hypertension); and it was difficult to elicit from the reporting which individual RCTs had been included and whether these overlapped with the RCTs in the other systematic reviews included in our analysis. The meta-analysis demonstrated a significant reduction in systolic (by 5.3 mmHg [95%CI 3.4 mmHg to 7.2 mmHg]) and diastolic (by 3.1 mmHg [95% CI 1.7 mmHg to 4.5 mmHg]) blood pressure with increased potassium intake (either diet or supplementation) compared with control in patients with hypertension. [47] Reductions in blood pressure were noted at 90-120 mmol/day of potassium. Reductions were seen with both increased dietary potassium intake and potassium supplementation. The analysis also identified no increased lipids or deterioration of renal function from the available data.

Clinical guide

The evidence for potassium supplementation shows that it may reduce blood pressure, especially among hypertensive patients and those consuming a high-salt diet. As with any other potential treatment, the decision to increase potassium intake or begin potassium supplements should be discussed initially with a healthcare worker. Careful follow-up and monitoring is required. Increased potassium intake should be used with caution in patients with chronic kidney disease, those who have high-normal potassium levels, or in those already taking medications that will raise potassium. There is no current evidence favouring combinations of supplements with potassium, calcium, or magnesium to lower blood pressure given the paucity and significant heterogeneity of existing trials.

In addition, the Dietary Approaches to Stop Hypertension (DASH) diet, which is widely recommended in people with hypertension, is rich in potassium, calcium, and magnesium and low in sodium. If one follows a DASH diet, the incremental benefit of superimposed potassium supplementation is unknown. [48]

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Mediterranean-style diet New option. One systematic review added. [25] Categorised as 'likely to be beneficial'.

Low-salt diet (including the DASH diet) One systematic review updated. [29] Two RCTs added. [30] [31] Categorisation unchanged as 'likely to be beneficial'.

Magnesium supplementation One systematic review updated. [42] Categorisation unchanged (unknown effectiveness).

Potassium supplementation One RCT added. [46] Categorisation changed from 'unknown effectiveness' to 'likely to be beneficial'.

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Competing interests: RP and DH declare that they have no competing interests. NK is a volunteer at Hypertension Canada, an organisation that promotes healthy eating and salt reduction, while ST is an AbbVie National coordinator for the SONAR study.
We would like to acknowledge the previous contributors of this review, including Joseph Cheriyan, Kevin M. O'Shaughnessy, and Morris J. Brown.

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TABLE GRADE evaluation of interventions for primary prevention of CVD: hypertension

Important outcomes	Mortality (all-cause and cardiovascular), cardiovascular events (MI, stroke, congestive heart failure, and coronary heart disease), renal outcomes, blood pressure, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of selected dietary modification for people with hypertension?									
2 (275) [25]	Blood pressure	Mediterranean diet *v* normal diet	4	0	–1	–1	0	Low	Consistency point deducted for heterogeneity in population characteristics; directness point deducted for borderline hypertensive baseline systolic and diastolic blood pressure in both RCTs and comorbidity with metabolic syndrome
24 (1520) [29] [30] [31]	Blood pressure	Salt reduction *v* normal intake	4	–1	+1	–2	0	Low	Quality point deducted for methodological flaws across RCTs; consistency point added for dose response; directness points deducted for uncertainty of diagnostic measurement in some studies and for use of an intervention in which sodium, potassium, and magnesium were supplemented (2 RCTs)
40 (at least 2492) [37] [38]	Blood pressure	Calcium supplementation *v* placebo or no supplementation	4	–1	–1	–1	0	Very low	Quality point deducted for poor follow-up; consistency point deducted for statistical heterogeneity among RCTs; directness point deducted for subgroup analysis in one SR
1 (65) [40]	Blood pressure	Calcium plus magnesium supplementation *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for borderline hypertensive baseline systolic blood pressure
18 (at least 545) [41] [42]	Blood pressure	Magnesium supplementation *v* placebo or no supplementation	4	0	–2	–1	0	Very low	Consistency points deducted for conflicting results and for statistical heterogeneity among RCTs; directness point deducted for subgroup analysis in one SR
23 (1756) [43] [44] [45] [46]	Blood pressure	Potassium supplementation *v* placebo or no supplementation	4	0	–1	–1	0	Low	Consistency point deducted for statistical heterogeneity among RCTs; directness point deducted for subgroup analysis in one SR
1 (60) [40]	Blood pressure	Potassium plus calcium supplementation *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for borderline hypertensive baseline systolic blood pressure
3 (277) [39]	Blood pressure	Potassium plus magnesium supplementation *v* control	4	0	–1	0	0	Moderate	Consistency point deducted for statistical heterogeneity among RCTs

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.